Rituximab maintenance after autologous stem cell transplantation in relapsed patients with CD20+ diffuse large B-cell lymphoma (DLBCL): CORAL final analysis

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Appendix document 1 according to protocol: http://coral.gela.org/

Statistics

Statistical analysis was planned and performed as follows:

Descriptive statistics

Patient characteristics were compared between the two treatment arms using the Pearson chi 2 or the Fisher exact test. Study end points were CR and PR rate, event-free survival (EFS), progression-free survival (PFS), and overall survival (OS). Patients without progression or relapse who were still alive were censored at the date of last contact.

Quantitative variables were summarized in tables displaying sample size, mean, standard deviation, median, range; quartiles were presented when considered relevant.

Qualitative variables were described in terms of frequencies of each response category and frequencies were converted into percentages of the number of patients or adverse events examined depending on the statistical unit under investigation.

Censored data were presented as Kaplan-Meier plots of time to first event and summary tables of Kaplan-Meier estimates for criterion rates at fixed time points with 95% CIs. The median time to event was calculated (if reached) with 95% CIs. Estimates of the treatment effect were expressed as hazard ratios based on Cox regression with 95% confidence intervals.

Statistical inference

Statistical tests were two-sided and performed using a 5% level of significance. When relevant, 95% confidence intervals were also presented. Survival endpoints were analyzed using the log rank test (unstratified), the Cox model for corresponding hazard ratios, p-values of treatment effects, multivariate models with 95 percent confidence intervals and *P* values based on the likelihood ratio test in unadjusted and adjusted analysis.

The number and proportion of responders and non-responders in each treatment group together with the two-sided 95% Pearson-Clopper CI were presented, as well as the difference between the proportions, the two-sided 95% asymptotic confidence interval and the p-value of a chi-square test.

All statistical analyses were carried out with SAS 9.1.3 software (SAS Institute, Cary, NC).

Determination of sample size

Part I induction:

The primary endpoint was mobilization adjusted response rate after three cycles of chemotherapy, and it was expected that to detect a difference in mobilization adjusted response rate of 15% between R-ICE 60% (75% response rate and 15% mobilization failure) and R-DHAP 45% (65% response rate and 20% mobilization failure) with 82% power at the 5% significance level, 400 patients should be randomized between the two chemotherapy arms. Initially, 400 patients were randomized 1:1 to either R-ICE or R-DHAP.

It was expected that 40% of these patients would either not achieve Complete Response or Partial Response or would drop-out before ASCT. It was expected that there would be 240 patients (400 x 60%) available immediately prior to ASCT for the second randomization (1:1) into the maintenance or rituximab arms. First safety analysis on 100 patients (reviewed by DSMC on 14th November 2005) and first interim analysis on 200 patients (18th April 2007) showed that the drop-out rate was 50%. Then, in order to keep the planned power with 240 patients for the maintenance or rituximab arms, we increased the initial sample size from 400 to 480 (240 each). The enrolment was completed in June 2008.

Part II maintenance:

The primary endpoint of event-free survival (EFS) was used to assess sample size. If we wished to detect after transplantation a change in the 2 year event-free survival of 15% in favor of the rituximab arm (65%) versus no maintenance (50%), 240 transplant patients randomized 1:1 between the two treatment groups recruited over three years and followed for a minimum of two years will provide 80% power to detect the expected difference at the overall 5% (2-sided) significance level.

Interim analysis

An interim analysis of the two parts, response rate and EFS efficacy parameters was planned after 200 patients, necessitating an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O'Brien-Fleming adjustment will be used to partition the α-level with α=0.003 at the first interim for response and α=0.05 at the final analysis.

An interim analysis of the primary efficacy parameter was planned after the inclusion of 200 patients leading to 100 patients randomized to the maintenance treatment. This necessitates an adjustment of the nominal significance (α-level) for the final analysis to maintain the overall global significance level. The O'Brien-Fleming adjustment will be used to partition the α-level with $\alpha=8.10^{-5}$ (40 events) at the first interim and $\alpha=0.05$ at the final analysis. The expected number of events during the five years is 140 to 145.

It was expected that 40% of these patients will either not achieve Complete Response or Partial Response or drop-out before ASCT. Immediately prior to ASCT it was expected that there will be 240 patients (400 x 60%) available for second randomisation (1:1) into the maintenance or mabthera arms. First safety analysis on 100 patients (reviewed by DSMC on 14th November 2005) and first interim analysis on 200 patients (18th April 2007) showed that the drop-out rate is 50%. Then, in order to keep the planned power with 240 patients for the maintenance or mabthera arms, we increase the initial sample size from 400 to 480 (240 each)

The whole set of 481 patients was first randomized from July 24, 2003 to June 30, 2008 (approximately five years of enrollment). 245 patients were then randomized in the 2nd part of the study from October 21, 2003 to October 21, 2008.

Follow-up

Stopping date was set to June 1, 2010 since last event occurred on this date. 92% of patients had a date of last contact after September 1, 2009.

Primary criterion

The aim of the 2nd part of the study was to evaluate the efficacy of rituximab given every eight weeks starting at day 28 after ASCT for a maximum of 6 doses in comparison to observation as measured by the event-free survival (EFS), events

defined as death from any cause, relapse for complete responders and undocumented complete responders, progression during or after treatment, changes of therapy during allocated treatment.

140 events were required to conclude. Nevertheless, due to low rate of events since more than one year, analysis is performed with 111 events.

Efficacy evaluation

Eligible patients for analysis

Five populations of patients were identified:

- ✓ ***Induction full analysis set*** (following the intent-to-treat principle) refers to all randomized patients regardless they have received study treatment or not: 477 patients analyzed according the therapy they were randomized to receive (243 in R-ICE arm and 234 in R-DHAP arm).
- ✓ ***Induction Intent-To-Treat (ITT) population*** refers to patients receiving at least one injection of study treatment, regardless the quantity injected: 469 patients analyzed according the therapy they were randomized to receive (239 in R-ICE arm and 230 in R-DHAP arm).
- ✓ ***Induction safety population*** refers to patients receiving at least one injection of study treatment: 469 patients analyzed according the therapy they actually received (239 in R-ICE arm and 230 in R-DHAP arm).
- ✓ ***Maintenance Intent-To-Treat (ITT) population*** refers to all patients formally randomized in the 2nd part of the study: 242 patients analyzed according the therapy they were randomized to receive (122 in rituximab arm and 120 in observation arm).

- ✓ ***Maintenance safety population*** refers to all patients formally randomized in the 2nd part of the study and have received at least one dose of rituximab or have only been observed, and have at least one maintenance follow-up assessment: 235 patients analyzed according the therapy they actually received, i.e. patient will be included in rituximab arm if he/she had received at least one dose of rituximab during any maintenance visit otherwise, he/she will be included in observation arm (thus, 116 in rituximab arm and 119 in observation arm).

Since all patients received randomized induction treatment, induction ITT and safety populations are equivalent.

Appendix document 2:

Data monitoring and regulatory aspects

Investigators

This was an Intergroup Study. The participating Groups are GELA (Groupe d'Etude des Lymphomes de l'Adulte) from France, Belgium, DSHNHL (German High Grade NHL), NCRI (National Cancer Research Institute) from the United Kingdom, ALLG (Australasian Leukemia Lymphoma Group) from Australia and New Zealand, SAKK (Swiss Group for Clinical Cancer Research) from Switzerland, centers from Sweden and Ireland, MSKCC (Memorial Sloan Kettering Cancer Center) from the USA, CLSG (Czech Lymphoma Study Group), and ISH (Israel Society of Hematology).

Participating centers were determined by each Lymphoma group, and participation was restricted to transplant centers. Local organization of care within the network of the group was authorized as long as GCP procedures could be followed. Before any inclusion, each center must have received an Ethical Committee approval for this study and government authorization according to procedures in each country. To be declared as a participating center, the respective principal investigator must have sent to the international coordinator his *curriculum vitae.*

Sponsor and study coordination center

Sponsor: GELARC- CORAL Collaborative Trial in Relapse/ Refractory Aggressive Lymphoma

This was an Intergroup Collaborative Study organized by a Steering Committee including the principal investigator of each study group. The steering committee will be represented by an intergroup protocol coordinator to organize the study. The study therefore shall be conducted under the sponsorship of the collaborative groups as mentioned and specified in the protocol: GELA, NCRI, DSHNHL, ALLG, Sweden, Ireland and US centers, hereinafter referred to as CORAL "Collaborative Group." The principal investigator of each individual collaborative group was responsible for answering all clinical questions concerning eligibility, treatment and evaluation of the patients and for study coordination within his group (administrative procedures, Ethics Committee approval, SAE-reporting to local authorities) in collaboration with a local investigator. The principal investigator of the group was in communication with

the coordinating center (GELA-RC) and the protocol coordinator. In case of absence, another coordinator should be designated by the group.

All participating countries had to sign an agreement with the sponsor GELARC describing duties, flow of data and responsibilities. The data were analyzed and centralized at the GELARC data center in Lyon.

The steering committee will be responsible for running the study with the protocol coordinator; it will give its scientific advice during the study and in the elaboration of data reports (manuscripts, speakers, ancillary research…).

Study coordination center: GELA-RC (groupe d'étude de l'adulte- recherche Clinique)

Although each group was responsible for the organization within its center, general coordination on time was necessary as well as centralized data management. GELA-RC structure will act as the coordination center. GELARC is located in France: Paris StLouis, for randomization and part of the data, Lyon Sud for another part of the data management and statistical analysis. The data were collected by the principal investigator at each participating center, checked for accuracy in each country by the coordinator and research assistants of the lymphoma group, and sent to GELA RC. Queries were sent to each country coordinator and data entry was performed after resolution. Its role is outlined here:

Randomization procedure

Distribution and collection of CRF in collaboration with study group principal investigator

Data entry and validation

Elaboration and mailing of queries

Reporting of Serious Adverse events (see chart)

Coordination of response review

Coordination of histological review

Coordination of monitoring procedures for each group

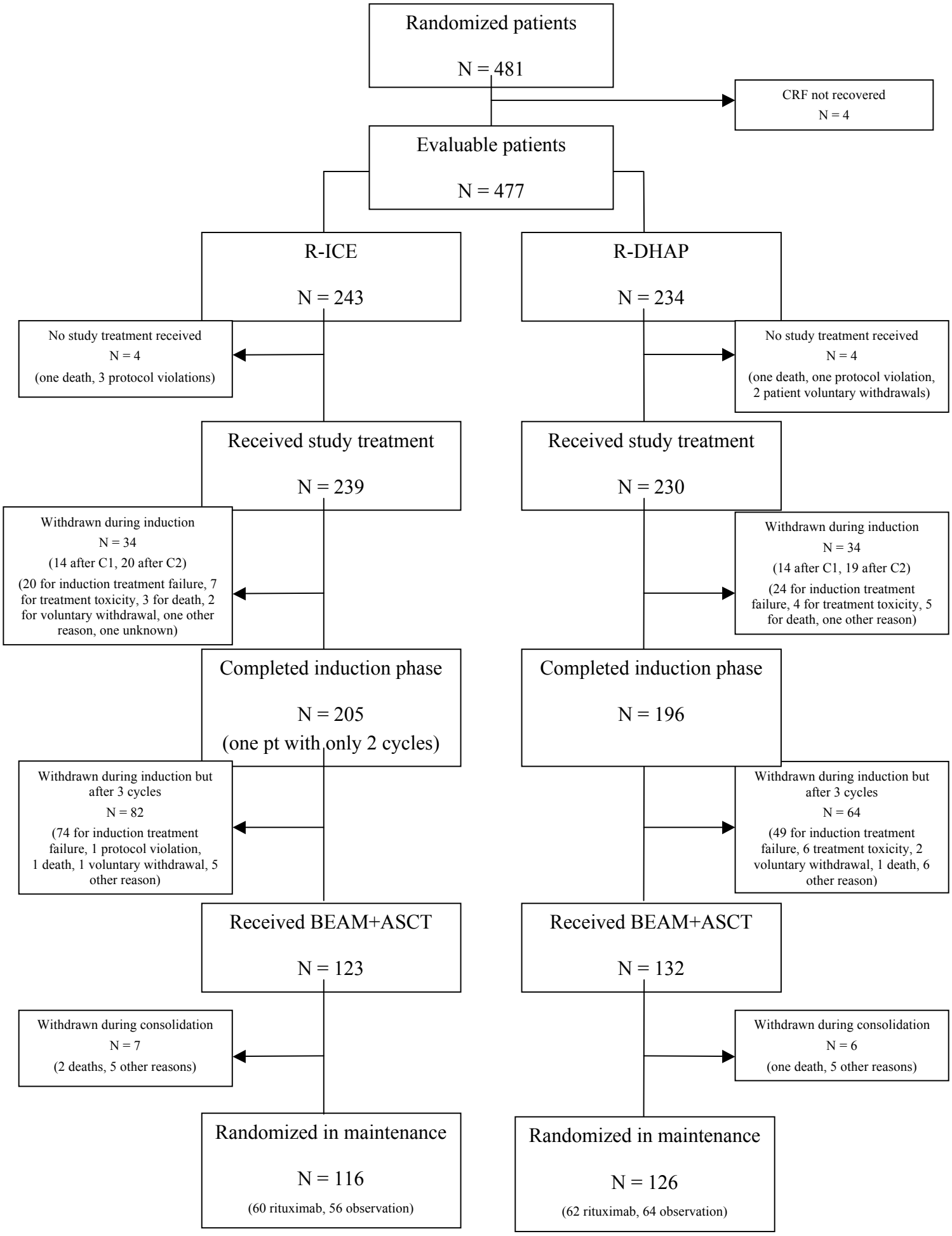
Relation with investigators and newsletter

Transmission of their data to the group on a regular basis

Statistical analysis, report

Any demand from the steering committee

Consort Figure -1 Disposition of patients according to arm of 1st randomization



Appendix table 1: Baseline characteristics of the patients (intent to treat)

	R-ICE (N=243)	R-DHAP (N=234)	P value
Age			
Median yr	50 y	52 y	
Range yr	19-65	19-65	ns
Sex Male	156	147	
Female	87	87	ns
Ann Arbor stage			
Stage I-II	93	89	
Stage III-IV	149	143	ns
ExtraNodal Site > 1	67	78	ns
Bone marrow involvement	21	22	ns
Elevated LDH	126	117	ns
Age-adjusted prognostic index at relapse			
saaIPI 0-1	142	139	
saaIPI 2-3	93	88	ns
Time to relapse			
<12 months *	104	99	ns
≥12 months	138	131	
Prior rituximab treatment	155	151	ns
Prior 1st line chemotherapy			
CHOP-like	203	203	ns
Intensified CHOP	32	27	

Abbreviations:

EFS, event free survival; PFS, progression free survival; OS, overall survival.

R-ICE: rituximab, ifosfamide, carboplatin, etoposide

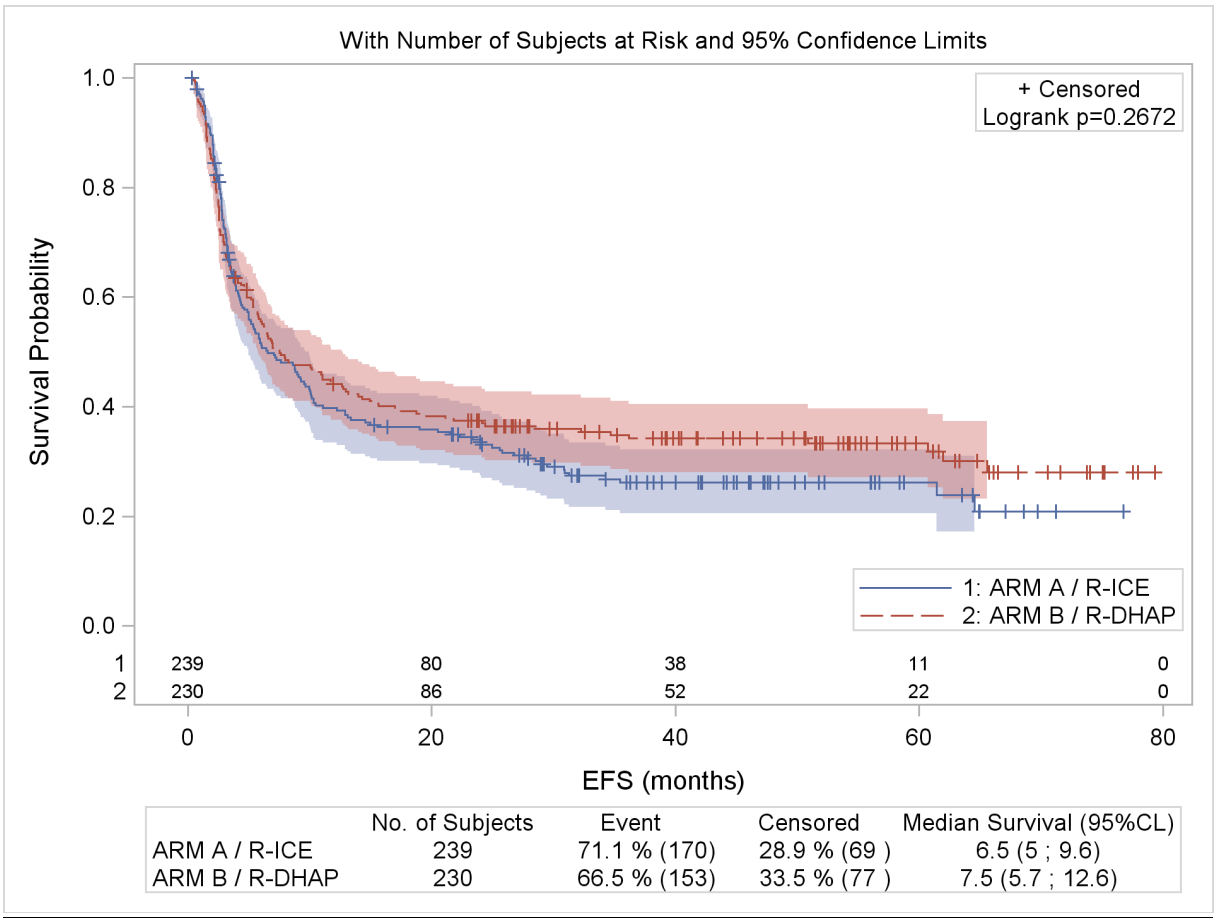
R-DHAP: rituximab dexamethasone, aracytine, cisplatin

CHOP: cyclophosphamide, doxorubicin,vincristine,prednisone

LDH:lactatdehydrogenase; ns: not significant,

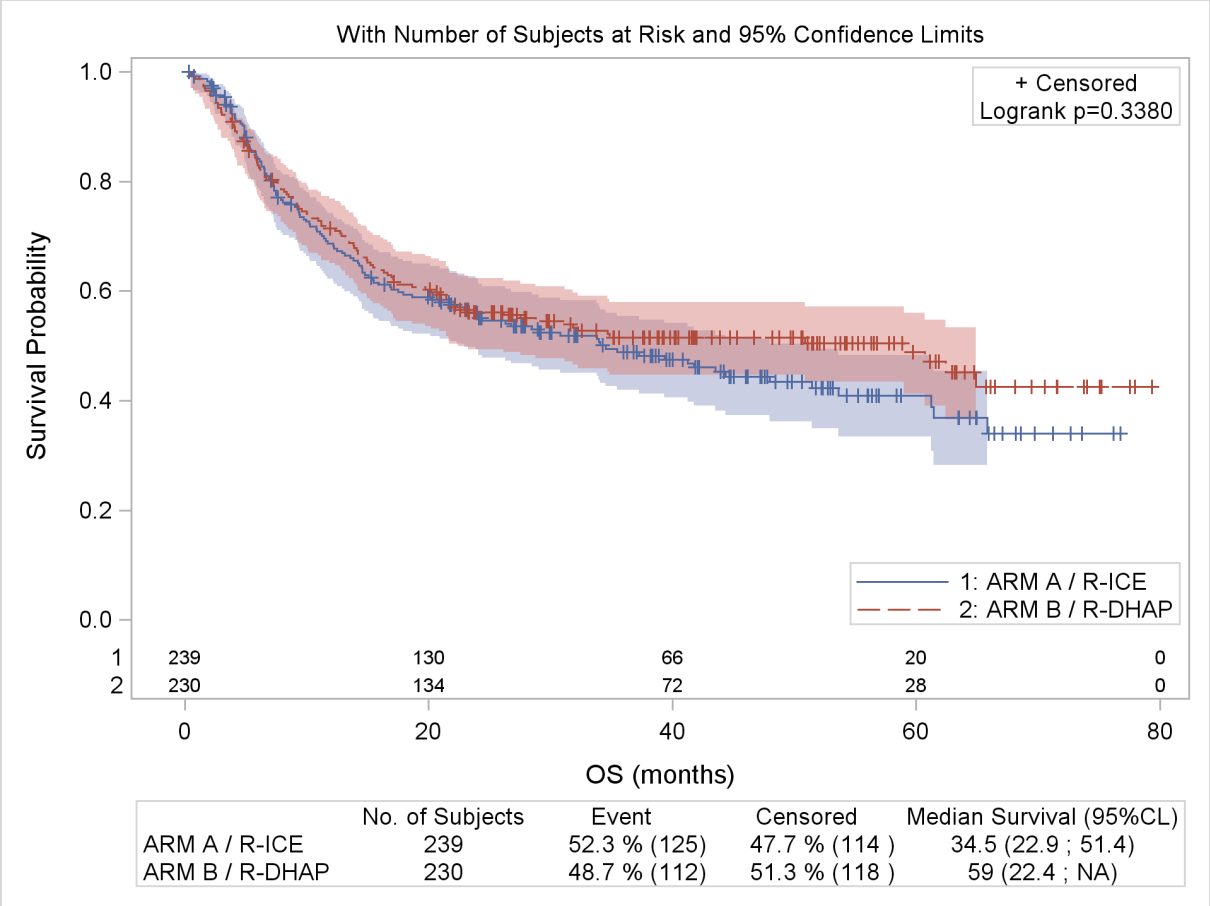
saaIPI: secondary age-adjusted international prognostic index at relapse.

Figure 2a: Secondary criteria – Event-Free Survival according to treatment arm from induction treatment.



	No. of Subjects	Event	Censored	Median Survival (95%CL)
ARM A / R-ICE	239	71.1 % (170)	28.9 % (69)	6.5 (5 ; 9.6)
ARM B / R-DHAP	230	66.5 % (153)	33.5 % (77)	7.5 (5.7 ; 12.6)

Figure 2b: Secondary criteria – Overall Survival according to treatment arm (induction ITT)



	No. of Subjects	Event	Censored	Median Survival (95%CL)
ARM A / R-ICE	239	52.3 % (125)	47.7 % (114)	34.5 (22.9 ; 51.4)
ARM B / R-DHAP	230	48.7 % (112)	51.3 % (118)	59 (22.4 ; NA)

Appendix table 2: Response rate according to prognostic factors (ORR: CR+ Cru+ PR) was 63 % (57.2-69.7) in R-ICE arm and 64 % (57.8-70.5) in R-DHAP arm.

The mobilization adjusted response rate is 51.5% in R-ICE arm vs 56.5% in R-DHAP arm (p=0.27).

Exploratory analyses – Overall response rate according to prior rituximab and failure from diagnosis (induction ITT)

	Prior treatment with Rituximab							
	No				Yes			
	Failure from diagnosis				Failure from diagnosis			
	< 12 months		>= 12 months		< 12 months		>= 12 months	
	N	%	N	%	N	%	N	%
Response after complete induction								
CR/CRu/PR	28	64	108	88	107	46	57	81
Other	16	36	15	12	125	54	13	19
Total	44	100	123	100	232	100	70	100

Appendix**:** Table 3: Relative Risk (RR) estimates for PFS in Male vs Female according to Rituximab, age and Body mass Index (BMI)

	Female	**Male**	**RR (M vs F)**	**P value**
Observation	37	83	1.19	0.56
Rituximab	46	76	2.43	0.006
Rituximab				
<50 years	17	28	2.35	0.019
≥50 years	29	48	2.43	0.015
Rituximab and ≥50 years				
BMI ≥25	14	32	1.55	0.30
BMI <25	15	16	4.13	0.03

Figure 3a: Progression free, survival according to age > 50 years in rituximab arm

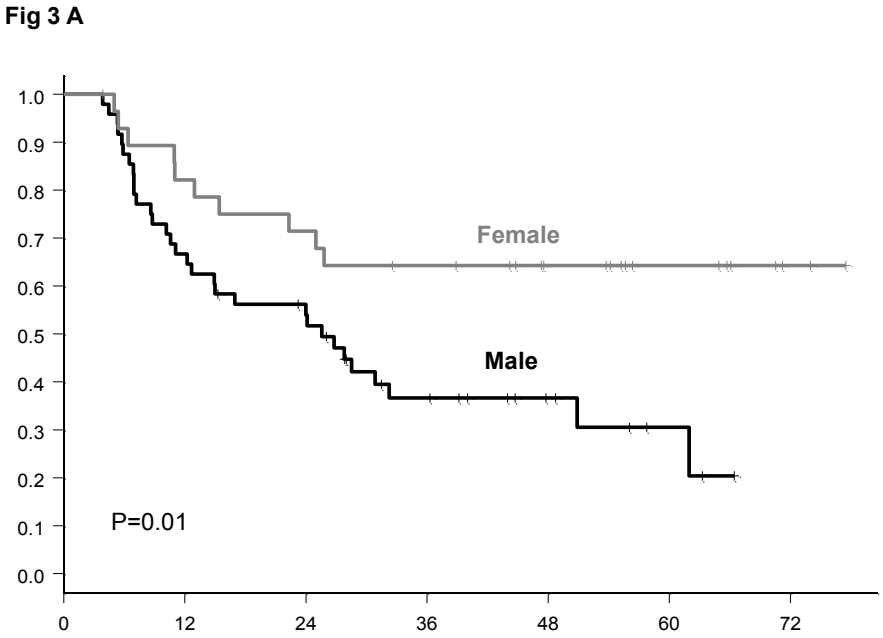


Figure 3b Progression free, survival according to age > 50 years and body mass index > 25 in rituximab arm

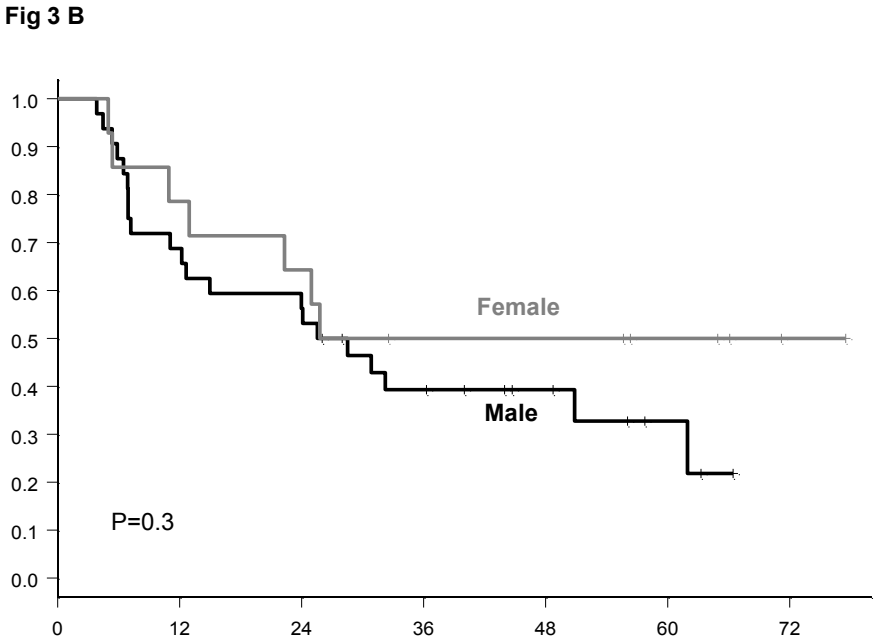


Figure 3c Progression free, survival according to age > 50 years and body mass index < 25 in rituximab arm

Fig 3 C

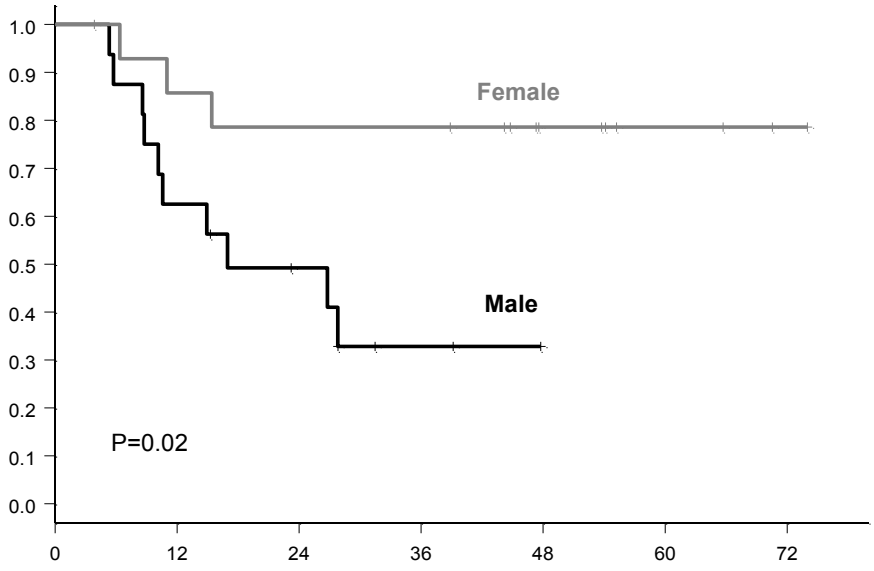
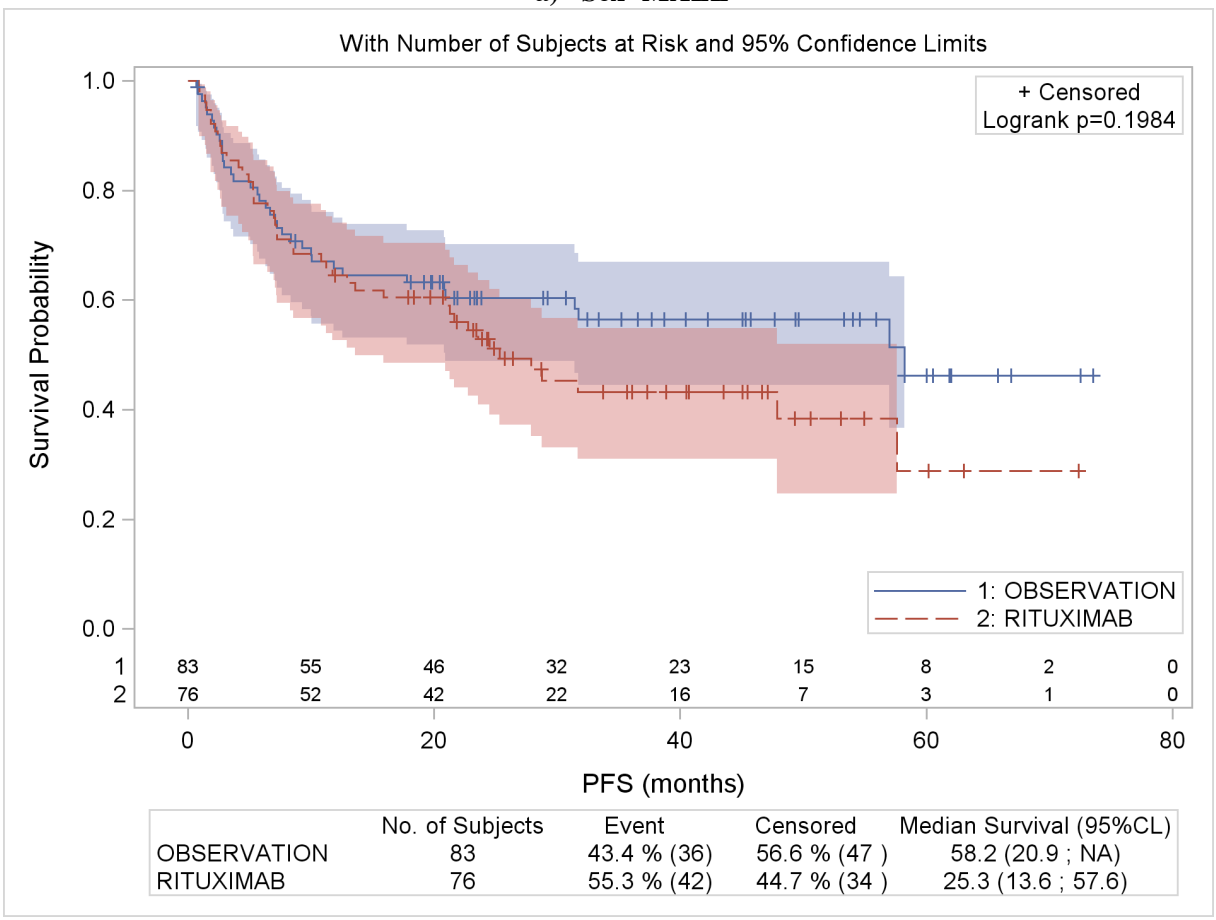
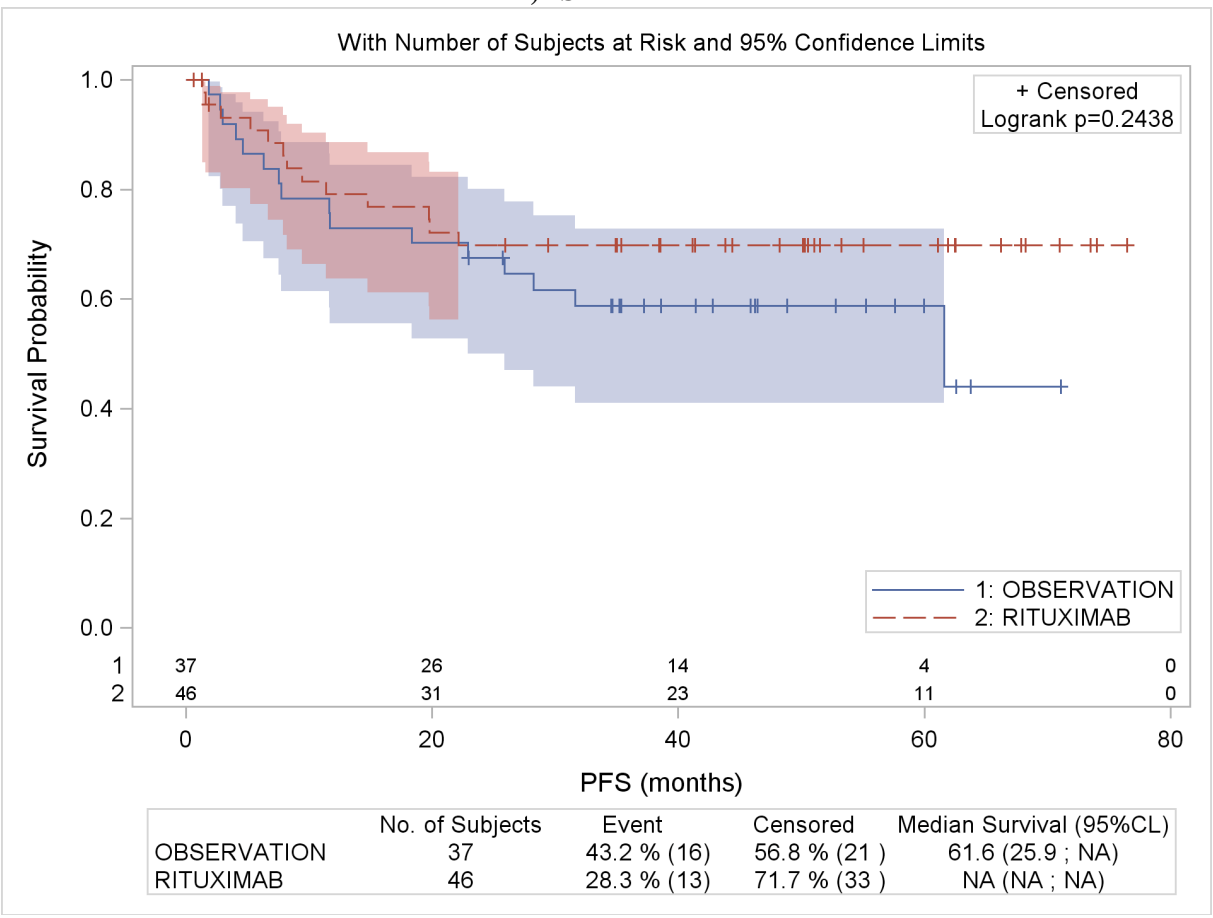


Figure 4a, b: Progression free survival * (EFS) according to the second randomization and treatment arm rituximab or observation

a) Sex=MALE



b) Sex=FEMALE



	No. of Subjects	Event	Censored	Median Survival (95%CL)
OBSERVATION	37	43.2 % (16)	56.8 % (21)	61.6 (25.9 ; NA)
RITUXIMAB	46	28.3 % (13)	71.7 % (33)	NA (NA ; NA)

Table 4 CORAL study
Cox models - maintenance population (excluding SD patients)
PFS from 2nd randomization

Analysis of Maximum Likelihood Estimates								
Parameter	**DF**	**Parameter Estimate**	**Standard Error**	**Chi-Square**	**Pr > ChiSq**	**Hazard Ratio**	**95% Hazard Ratio Confidence Limits**	
Arm of 2nd randomization RITUXIMAB	1	0.13214	0.20672	0.4086	0.5227	1.141	0.761	1.711
Age-adjusted IPI 2-3	1	0.74159	0.20798	12.7139	**0.0004**	2.099	1.396	3.156
Sex MALE	1	0.58717	0.23223	6.3926	**0.0115**	1.799	1.141	2.836
Prior treatment with Rituximab No	1	-0.17526	0.22847	0.5884	0.4430	0.839	0.536	1.313
Failure from diagnosis < 12 months	1	0.19620	0.23001	0.7276	0.3937	1.217	0.775	1.910
Response after complete induction PR	1	0.14102	0.20908	0.4549	0.5000	1.151	0.764	1.735
Arm of treatment ARM A / R-ICE	1	0.38543	0.20591	3.5038	0.0612	1.470	0.982	2.201

Table 5 : Progression/relapse n°1 – Type of progression/relapse treatment (MITT)

	Arm of 2nd randomization			
	RITUXIMAB		OBSERVATION	
	N	%	N	%
Chemotherapy				
Not Done	0	0	1	2
Yes	35	80	32	73
No	9	20	11	25
Radiotherapy				
Not Done	0	0	1	2
Yes	12	27	15	34
No	32	73	28	64
Immunotherapy				
Not Done	0	0	1	2
Yes	10	23	12	27
No	34	77	31	70
Transplantation				
Not Done	0	0	1	2
Yes	11	25	4	9
No	33	75	39	89
Other treatment				
Not Done	0	0	1	2
Yes	8	18	5	11
No	36	82	38	86
Total	44	100	44	100